Cost-effectiveness of the alternative uses of polyvalent meningococcal vaccines in Niger: an agent-based transmission modeling study

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Funding: Financial support for this study was provided by a contract with PATH (https://www.path.org/) and by awards 1K01AI119603 from the National Institute of Allergy and Infectious Diseases (https://www.niaid.nih.gov/), U54GM088558 from the National Institute of General Medical Sciences (www.nigms.nih.gov), and a scholarship from the German Research Foundation (DFG) (http://www.dfg.de). The funding agreement ensured the authors' independence in designing the study, interpreting the data, writing, and publishing the report.

Abstract

Background Despite the introduction of an effective serogroup A conjugate vaccine (*MenAfriVac*^{TM}), sporadic epidemics of other *Neisseria meningitidis* serogroups remain a concern in Africa. Polyvalent meningococcal conjugate (PMC) vaccines may offer alternatives to current strategies that rely on routine infant vaccination with *MenAfriVac*^{TM} plus, in the event of an epidemic, district-specific reactive campaigns using polyvalent meningococcal polysaccharide (PMP) vaccines.

Methods We developed an agent-based transmission model of *N. meningitidis* in Niger to compare the health effects and costs of current vaccination practice and three alternatives. Each alternative replaces *MenAfriVac*^{TM} in the infant vaccination series with PMC and either: replaces PMP with PMC for reactive campaigns or implements a one-time catch up campaign with PMC for children and young adults.

Results Over a 28-year horizon, replacement of *MenAfriVac*^{TM} with PMC in the infant immunization series and of PMP in reactive campaigns would avert 63% of expected cases (95% prediction interval 49-75%) if elimination of serogroup A is not followed by serogroup replacement. At a PMC price of $4/dose, this would cost $1412 ($81-$3,510) per disability adjusted life year (DALY) averted. If serogroup replacement occurs, the cost-effectiveness of this strategy improves to $662 (−$654, $2,473) per DALY averted. Sensitivity analyses accounting for incomplete laboratory confirmation suggest that a catch-up PMC campaign would also meet standard cost-effectiveness thresholds.

Limitations A simplifying assumption that polyvalent vaccines offer similar protection against all serogroups.

Conclusions Use of PMC vaccines to replace *MenAfriVac*^{TM} in routine infant immunization and in district-specific reactive campaigns would have important health benefits and are likely to be cost-effective in Niger. An additional PMC catch-up campaign would also be cost-effective if we account for incomplete laboratory reporting.

Introduction

The meningitis belt, a region is Sub-Saharan Africa with an estimated population of 430 million people, is prone to sporadically occurring meningitis epidemics [1-3]. These epidemics place a heavy burden on national and local resources [4], resulting in substantial deaths and long-term disabling sequelae [5]. The largest of these epidemics caused an estimated 250,000 cases with more than 25,000 deaths in 1996 [6, 7]. For the past 30 years, control of meningitis epidemics in this region has relied on reactive vaccination campaigns using polysaccharide vaccines in districts where the weekly meningitis incidence passes a critical incidence threshold of 10/100,000 population [4, 8, 9]. While this strategy, when deployed early in an epidemic, could save lives, it has not reduced the frequency and magnitude of epidemics because (1) polysaccharide vaccines induce only short-term protection (especially in children) [4, 10, 11], and (2) the successful implementation of reactive vaccination campaigns is hampered by significant delays between outbreak identification and vaccination responses [12, 13].

The introduction of a *Neisseria meningitidis* serogroup A conjugate meningococcal vaccine (PsA-TT, *MenAfriVac*™) in the African meningitis belt in 2010-11 has reduced meningitis A carriage and cases to an exceptionally low level [3, 14-17]. Despite the early success of *MenAfriVac*™ in the prevention of meningitis A epidemics, other non-A serogroups continue to cause epidemics of meningitis [9, 18-21]. Examples include the *N. meningitidis* serogroup W epidemic in Burkina Faso (2012) [22], the *N. meningitidis* serogroup X epidemics in Burkina Faso (2010), Niger (2006), and Togo (2009) [23, 24], and a recent severe epidemic by a novel strain of *N. meningitidis* serogroup C (NmC) in Niger (2015) [25, 26], as well as the largest ever recorded epidemic of NmC in Nigeria (2017) with more than 14,000 suspected cases [26, 27].

To combat the remaining threat from non-A meningococcal serogroups, polyvalent vaccines that target C, Y, W, and X serogroups (in addition to A) are being considered for use in Africa [12, 21, 25, 28, 29]. In contrast to the available polyvalent meningococcal polysaccharide (PMP) vaccines, polyvalent meningococcal conjugate (PMC) vaccines are immunogenic in young children and induce longer-term (10-15 year) protection, and hence, can also be used in reactive and/or mass preventive vaccination campaigns [2, 30-32] as well as in the Expanded Program on Immunization (EPI).

A recent cost-effectiveness analysis in Burkina Faso suggests that a vaccination strategy that involves a catch-up nationwide vaccination campaign in young adults with PMC vaccine and the addition of this vaccine to EPI (as a replacement for *MenAfriVac*™) will likely be cost-effective compared with the current World Health Organization (WHO) strategy of reactive vaccination using PMP vaccines [33]. Yet, the evidence to inform the best use of these novel polyvalent meningococcal vaccines for other countries of the meningitis belt is lacking. Despite similarities in certain characteristics of meningococcal epidemics across countries of meningitis belt [10, 29], the difference in population sizes and structures, age-distribution of meningococcal cases, and carriage prevalence may impact the performance of vaccination strategies from one setting to another [17].

In this study, we describe a district-level, agent-based model (ABM) of meningococcal transmission in Niger. While Niger has a similar total population size as Burkina Faso, the population density of Niger is considerably

lower (with largest concentrations of individuals in southwestern districts) and Niger has experienced less severe meningococcal epidemics since 2002. As vaccination programs may offer relatively smaller health gains in settings with less severe meningococcal epidemics, the evaluation of PMC vaccination strategies in Niger, and comparison with previously reported results from Burkina Faso, will shed light on how the local epidemiology of disease affects the projected health impact and costs associated with alternative vaccine strategies.

Methods

An Agent-Based Model Meningococcal Transmission in Niger

Our ABM is a stochastic, and spatially-explicit model [34-36] to describe the meningococcal transmission across 44 districts of Niger (Figure 1 and Figure S2). Meningitis epidemics in Niger (along with other countries of meningitis belt) occur sporadically and, when they do occur, are of greatly varying severity (Figure 2) [21, 37, 38]. This suggests that a stochastic model can best simulate the types of chance events that ultimately lead epidemic take-off or fade-out after the appearance of meningitis cases within a district.

Capturing meningococcal epidemics at district level is necessary to model reactive vaccination campaigns that are triggered when districts exceed the WHO epidemic threshold of 10 per 100,000 population in a week [4]. We employed a gravity model to approximate the age-specific intensity of contacts among individuals within and between districts (see Appendix).

Our ABM is based on existing mathematical models developed for different countries of the meningitis belt [20, 33, 39-41] but allows for additional flexibility to represent complex vaccination strategies and the sequential timing of events experienced by individuals. In contrast to compartmental models where the change in size of each compartment is tracked over time, ABMs tracks each population member separately. For our study, this allows us to 1) model the variation in cost and health outcome across individuals and 2) to more accurately describe the individual-level impact and population-level implementation of vaccine strategies (as described below).

In our ABM, individuals are assumed to be in one of four health states at any given time: Susceptible, Carrier, Meningitis, and Immune (Figure 1). Susceptible individuals are at dynamic, age-specific risk of infection with *N. meningitidis* that is proportional to the prevalence of invasive meningitis and carriage. Infected individuals move to an asymptomatic but infectious state ("Carrier") where they may develop invasive meningitis disease ("Meningitis"), or lose their carriage status and develop immunity ("Immune"). The rate of progression to the active disease is highest at the time of infection and decreases gradually over time such that only a small portion (around 1%) of carriers eventually develop meningitis. Individuals who lose their carriage state or recover from meningitis will develop immunity against reinfection. The duration of this immunity is assumed to be shorter for those who acquired their immunity through the loss of carriage state compared with those who become immune after recovering from meningitis disease. We also assume that the probability of superinfection while in carriage

state is negligible. Further details about the model assumptions and parameters as well as the demographics of Niger are provided in the Appendix.

Data Sources

To parameterize our model, we used an anonymized dataset of all documented clinical meningitis cases in Niger from 2002 to mid-2015 (provided by the Ministry of Health, Niger). The dataset contains sample date, district, age, and the final clinical diagnosis for 29,349 clinical cases. To use this dataset to calibrate our simulation model, we categorized each reported meningitis case into one of six mutually-exclusive groups based on the final clinical diagnosis (Table 1). For reported cases where laboratory typing was not completed (n = 5,089), we use empirical distributions of the serogroup-distribution of each epidemic season to assign a meningitis type, assuming that these case designations were missing at random. Using this dataset, we estimated the weekly *N. meningitidis* cases by serogroup and age group within districts of Niger, which was then used to calibrate our model (see below).

Analyzing this dataset shows that in districts where epidemics were detected between 2002-2015, the majority of reported cases did not have a conclusive bacteriological diagnosis and were recorded as bacteriologically negative (Figure S6 in Appendix). Given the imperfect sensitivity of diagnostics, there is likely to be underreporting of meningococcal cases in this dataset as most meningitis cases (>79%) in epidemic years 2006-8 were caused by *N. meningitidis* [18]. Our projections of the cost-effectiveness of meningococcal vaccination strategies could underestimate the health benefits from vaccination programs if bacteriologically-confirmed cases significantly undercount the true burden of meningococcal meningitis. To account for this possibility, we consider two scenarios: 1) conservative scenario that assumes all meningococcal cases occurred in Niger from 2002 to mid-2015 are reported in our dataset and correctly categorized, and 2) an alternative scenario that assumes meningitis cases confirmed as *N. meningitidis* in our dataset represent only half of all meningococcal cases occurring in Niger during this period. We report the results of our cost-effectiveness analysis under both scenarios.

Strain-Replacement Scenarios

While the introduction of *MenAfriVac*™ has dramatically lowered serogroup A incidence in Niger [14, 17, 42], the possibility of serogroup A being replaced by other serogroups in the future still exists [18, 19, 21], as evidenced by yearly outbreaks and severe epidemic caused by a novel strain of serogroup C (NmC) in Nigeria in 2013-2015, and the largest ever recorded epidemic of NmC in Nigeria in 2017 [26]. As such, consistent with a similar cost-effectiveness study conducted for Burkina Faso [33], we consider two extreme scenarios to quantify the impact of serogroup-A replacement on the performance of vaccination strategies (Figure 2): (1) “Complete strain replacement” assumes that future epidemics will occur with similar frequency and magnitude as observed in Niger between 2002 to mid-2015, and (2) “No strain replacement” assumes that future will be similar to past with serogroup-A excluded. These two extreme scenarios bound the performance of vaccination strategies and allow us to investigate how robust the cost-effectiveness of vaccination strategies is with respect to the possibility of future strain-A replacement.

Model Calibration

We calibrated our ABM to capture the key characteristics of meningococcal epidemics under both strain replacement scenarios, including the age-distribution of meningococcal incidence (Figure 3A), average carriage prevalence among different age groups (Figure 3B), and weekly average incidence of meningococcal cases (Figure 3C) between 2002 to mid-2015 (the full duration of the available time series). We used the cosine of the angle (θ) between the vectors of Fourier amplitude for observed and simulated time-series of weekly meningococcal cases to measure how well the simulated trajectories match the periodicity of past meningococcal epidemics in Niger (Figure 3D). Figure 4 displays the time-series of meningococcal cases from three simulated trajectories over 30 years produced by the calibrated model in comparison with the meningococcal time-series observed in Niger during 2002-2015. We emphasize that our goal is not to fit to the *timing* of past epidemics but instead to calibrate the model against the *periodicity* of past epidemics in additional to calibration targets depicted in Figure 3. Details of our calibration approach are described in the Appendix.

Figure 5 suggests that our model behavior is consistent with the observed data on the *N. meningitidis* cases for all districts of Niger between 2002 and mid-2015. Reactive campaigns are launched in districts where weekly clinical meningitis incidence (which include not only confirmed meningococcal cases but also suspect cases of *H. influenzae* types b and non-b, and *S. pneumonia*) exceeds the WHO epidemic threshold of 10 per 100,000 population [12, 33]. Figure S9 in the Appendix confirms that our model's behavior at district level is consistent with the observed data of clinical meningitis cases on the number of years from 2002 to mid-2015 where each Niger district passes the WHO epidemic threshold.

Modeling the Impact of Vaccination

In our simulation model, we track the vaccination status of each individual by agent-level attributes. If individuals are vaccinated in the Susceptible state, their susceptibility to infection is reduced according to the effectiveness of the administered vaccine (Table 2). Vaccinated carriers are assumed to remain infectious but are protected from progression to the invasive disease for the duration of immunity offered by the vaccine. For those vaccinated while in the Immune state, if the natural immunity wanes sooner than the vaccine immunity, they proceed to the Susceptible state but remain partially protected against infection as long as the vaccine immunity lasts. We further assume that individuals with active meningitis are not eligible for vaccination, those vaccinated with PMP will become re-eligible for vaccination at the beginning of the next epidemic season, and those vaccinated with PMC would become vaccine eligible 10 years after the time of vaccination.

Alternative Vaccination Strategies

We estimate the cost and health outcomes of four vaccination strategies that differ by the types of vaccines used (*MenAfriVac*™, PMP, and PMC), the targeted age groups, and the vaccination programs (routine, reactive, and preventive) to immunize the population (Table 2). These policies are consistent with those considered in a recent cost-effectiveness study conducted for Burkina Faso [33]. The Base strategy represents the current WHO strategy

of using PMP vaccines in reactive campaigns at districts where weekly meningitis incidence passes the threshold of 10 cases per 100,000 population. As PMC vaccines offer protection against multiple serogroups (as opposed to *MenAfriVac*™ that induces immunity only against serogroup-A), and have better immunogenicity properties compared to PMP (Table 3), the Base strategy can be improved by replacing *MenAfriVac*™ in routine EPIs and PMP in reactive campaigns with PMC vaccines. This corresponds to the Base Prime strategy in Table 3.

Prevention 1 and 2 strategies immunize younger adults through mass nationwide immunization campaigns in addition to using PMC vaccines in EPI. We note that while the Base Prime strategy attempts to control district-level outbreaks, the two prevention strategies use nationwide campaigns to reduce the risk of infection and to potentially achieve herd immunity. We assume that preventive campaigns occur in November of the first simulation year and are completed before the start of the next epidemic season.

For reactive campaigns in Base and Base Prime strategies, once an epidemic is declared in a district, the time until the initiation of a reactive campaign is assumed to follow a discrete Uniform distribution of [2, 10] weeks [33]. Once triggered, reactive campaigns are assumed to continue until the end of the current season (although the majority of the district's population will get vaccinated within a few weeks after the vaccines are delivered).

Health and Financial Outcomes

We use disability-adjusted life-years (DALY) to measure the health outcomes associated with vaccination strategies. To measure the financial outcomes (presented in the US dollars), we consider disease-related costs incurred due to meningitis case management and care for patients who experience sequelae as well as costs of implementing vaccination campaigns. As the government and donors primarily bear the vaccination program costs in Niger, we adopt the payer's perspective in conducting cost-effectiveness analysis. All health and financial outcomes of alternative vaccination strategies are presented with respect to the Base strategy (Table 3) and discounted at an annual rate of 3% to 2016. Assumptions and details for health, financial outcomes, and DALY calculations are provided in the appendix.

We followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [43] to report the results of our cost-effectiveness analysis study. CHEERS is developed by ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force with the objective of optimizing the reporting of health economic evaluation studies. We present all estimates from the model as the average and 95% prediction intervals (the 2.5th and 97.5th percentiles) of 200 trajectories simulated over a 28-year period. We found that obtaining additional trajectories does not meaningfully change the bounds of the prediction intervals (see Figure S11).

Role of the Funding Source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study, and all authors had final responsibility for the decision to submit for publication.

Results

Replacing both *MenAfriVac*™ in routine EPIs and PMP in reactive campaigns with PMC vaccines (Base Prime strategy) results in 62% (46-77%) and 63% (49-75%) reduction in the annual meningococcal cases expected under the Base strategy for complete strain replacement and no strain replacement scenarios, respectively (Figure 6). This improvement is associated with superior immunogenicity of PMC vaccines compared to PMP vaccines (Table 2).

Base and Base Prime strategies both rely on reactive campaigns to response to epidemics and hence their performance would be impaired by logistical delays in the launch of these campaigns once the epidemic threshold is passed in a district. Our model shows that proactive strategies (i.e. Prevention 1 and 2) that aim to immunize young adults in mass vaccination campaigns avert the largest number of meningococcal cases: Prevention 1 averts 74% (54-99%) and 74% (58-99%) of cases, and Prevention 2 averts 79% (57-99%) and 79% (60-99%) of cases with respect to the Base strategy under complete strain replacement and no strain replacement scenarios. Our model suggests that none of these strategies results in elimination of *N. meningitidis* and the meningococcal epidemics may recur if reintroduction occurs after the herd immunity achieved through mass vaccination campaigns wanes.

Figure 7 shows the expected number of vaccines required for each vaccination strategy. Base and the Base Prime strategies have the highest and the lowest expected annual consumption of total vaccine doses, respectively, under both strain-replacement scenarios. For the Base strategy, the wide prediction intervals of the estimated number of PMP vaccines used are due to the sporadic district-level outbreaks that may trigger reactive campaigns in the affected districts. Since routine programs target 9 month infants, extending the vaccination projection horizon does not impact the estimated annual consumption of *MenAfriVac*™, PMP or PMC vaccines in routine programs. However, the extended horizon reduces the estimated annual consumption of PMC vaccines in reactive and preventive campaigns. This is because preventive campaigns are implemented only once at the beginning of the projection period.

We estimate the incremental cost-effectiveness ratio (ICER) of the Base Prime strategy with respect to the Base strategy to be $662 (−$654-$2,473) and $1,412 ($81-$3,510) for scenarios with and without strain A replacement. Per WHO recommendations, strategies that avert one DALY for less than three times the per capita gross domestic product are considered "cost-effective" [44]. Hence, at the cost-effectiveness threshold of $1,077, three per capita gross domestic product of Niger in 2015 [45], the Base Prime strategy is expected to be cost-effective with respect to the Base strategy under the complete strain replacement scenario. The ICER of Prevention 1 and 2 strategies is estimated to be above this cost-effectiveness threshold (Table 4). Prevention 1, however, remains a viable alternative as it is expected to cost $984 (−$180-$2,964) and $1,779 ($516-$4,007) per DALY averted with respect the Base strategy under with and without strain A replacement scenarios (Figure 8A-B).

Figure 8C-D compare the impact of vaccination strategies on the population's net monetary benefit (NMB) for varying values of the cost-effectiveness threshold (ω). The expected gain in NMB for a strategy with respect to

the Base strategy is calculated as: ω × (additional DALYs averted by the strategy) – (additional cost of the strategy). Prevention 1 and 2 demonstrate similar performance under both strain-replacement scenarios and the incremental benefit from all strategies are slightly larger when strain A elimination is followed by complete strain replacement (Figure 8 and Table 4).

The cost-effectiveness analysis results presented above (and in Figure 8 and Table 4) assume that all meningococcal cases that occurred from 2002 to mid-2015 in Niger are reported and correctly diagnosed in the patient-level dataset we used to calibrate our model. As demonstrated in Figure S6, this is a very conservative assumption and could lead to substantial underestimation of health benefits from meningococcal vaccination strategies. Under an alternative scenario that only 50% of cases caused by *N. meningitidis* are correctly diagnosed in our dataset (Figure S6), we estimate the cost-effectiveness ratios for Base Prime, Prevention 1 and Prevention 2 strategies with respect to the Base strategy at $395 (-$327-1,237), $563 (-$90-1,482) and $611 (-$27-1,537) under complete strain replacement and at $795 ($41-1,755), $986 ($258-2,003) and $1,046 ($317-2,159) under no strain replacement (Figure 9). As expected, under this scenario, the cost-effectiveness of the preventive catch-up vaccination strategies improves.

Additional sensitivity analysis shows that the cost-effectiveness of Base Prime and Prevention 1 and 2 strategies diminishes as the price of PMC vaccine increases (Figure S14). If PMC vaccine price is $10 per dose, we estimate the cost-effectiveness ratios for Base Prime, Prevention 1 and Prevention 2 strategies with respect to the Base strategy at $3,539 ($1,631-6,430), $3,988 ($1,932-7,455) and $4,139 ($2,139-7,677) under complete strain replacement and at $5,208 ($2,570-9,326), $5,809 ($3,010-10,272) and $6,017 ($3,223-10,608) under no strain replacement.

Discussion

The current WHO-recommended strategy for meningitis control in sub-Saharan Africa relies on using *MenAfriVac*™ in the EPI and PMP vaccines in districts where the epidemic threshold is passed. Our results indicate that once affordable PMC vaccines become available for Africa, this currently recommended strategy could be improved by alternative policies that rely on using PMC vaccines. A strategy that use PMC vaccines in the EPI and in reactive vaccination programs could offer a substantial improvement in reducing the meningococcal epidemics burden and is likely to be cost-effective at the PMC vaccine price of $4 or lower per dose. This strategy, however, still leaves district at risk of sporadic outbreaks. Augmenting this strategy with the addition of nationwide mass vaccination campaigns to immunize 1-18 year-olds with PMC vaccines could avert the majority of meningococcal cases. The cost-effectiveness of vaccination strategies that use PMC vaccine is improved if elimination of serogroup A is followed by a strain replacement. Accounting for incomplete laboratory confirmation also improves the cost-effectiveness of PMC vaccination, including catch-up campaigns.

A major strength of our study was the availability of a rich, individual-level dataset of more than 29,000 reported meningitis cases in Niger between 2002 to mid-2015. The availability of age, district and final diagnosis (due to

N. meningitidis serogroups as well as *H. influenzae* type b and *S. pneumoniae*) for reported cases and allowed us to calibrate our model against key properties of meningococcal epidemics in Niger. Our model demonstrates the ability to accurately describe the age-distribution of meningococcal cases and carriage prevalence as well as the discrete-level magnitude and frequency of meningitis activity. Moreover, while our model shares a similar structure to the existing compartmental models of African meningitis [20, 33, 39, 40, 46], the use of an agent-based modeling approach allowed for more accurate representation of disease natural history and evaluation of different vaccination strategies.

One of the limitations of our study stems from the assumption that polyvalent vaccines offer the same degree of protection against all serogroups. This assumption is consistent with existing models that aggregate serogroups into "vaccine" and "non-vaccine" type [33, 40, 47-49] and is also necessitated by the lack of data to characterize serogroup competition [40]. As polyvalent vaccines offer protection against all meningococcal serogroups, our model only describes the circulation of one 'vaccine' serogroup. This simplification may undermine the robustness of our model's results and its ability to project the frequency and magnitude of future meningitis epidemics, especially in the event that there is differential, serogroup-specific effectiveness of vaccines or complex between-serogroup interactions.

The vaccination strategies considered here can be compared with those we previously evaluated in a cost-effectiveness study of polyvalent meningococcal vaccines in Burkina Faso [33]. This previous study concluded that for Burkina Faso, vaccination strategies that rely on the use of PMC vaccines in EPI and also within catch-up prevention vaccination campaigns can be cost-effective (with respect to the current WHO strategy). The generalizability of this conclusion to other settings of the meningitis belt, however, was unclear. The findings presented here confirm that the conclusion that PMC vaccines can be used within vaccination strategies in a cost-effective manner when compared to the current WHO-recommended strategy also appears to be the case in Niger. However, in contrast to the situation in Burkina Faso, we note that preventive strategies (i.e. Prevention 1 and 2) were found to cost more per DALY averted with respect to the status quo in Niger (Table 4) than with respect to the status quo in Burkina Faso [33]. While there are differences in modeling approach between these analyses, we believe that the driving reason for the difference in the conclusion about the cost-effectiveness of the use of PMC in catch-up campaigns is that meningitis has been responsible for a far larger burden of disease in Burkina Faso (notifications of approximately 91,000 cases between 2005-2015) than in Niger (notifications of approximately 37,000 cases in this time period) [50].

The results of these cost-effectiveness analyses in Niger and Burkina Faso indicate a need to revisit the current WHO strategy for meningitis control in Sub-Sahara Africa, which relies on reactive campaigns using PMP vaccines, once affordable PMC vaccines are available. The cost-effectiveness of strategies to inform the use of PMC vaccines (e.g. to be employed in reactive vs. preventive campaigns) will differ across the countries of meningitis belt depending on the population distribution and the expected severity of meningococcal epidemics.

Acknowledgements

The authors gratefully acknowledge the generous assistance provided by Dr. Idrissa Maiga, Secretary General and Dr. Kadade Goumbia, Director, Surveillance et la Epidemic Response, Ministry of Health, Government of Niger, Niamey, Niger; Dr. Jean-Paul Moulia-Pelat, Centre de Recherche Medicale et Sanitaire (CERMES), Niamey, Niger; Dr. Assinawe Pana, WHO/WR, Niger, Clement Lingani, InterCountry Meningitis Unit, WHO/AFRO, Ouagadougou and Dr. Olivier Ronveaux, WHO/HQ, Geneva.

Figures

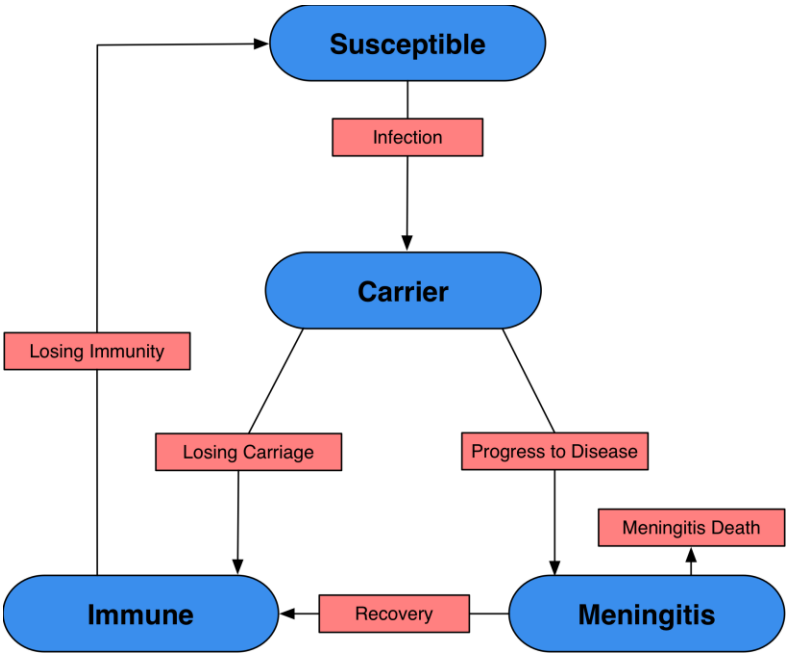

Figure 1: Model structure depicting health states (ovals) and health events (rectangles) for our agent-based model of meningococcal epidemics. Natural death may occur in any state.

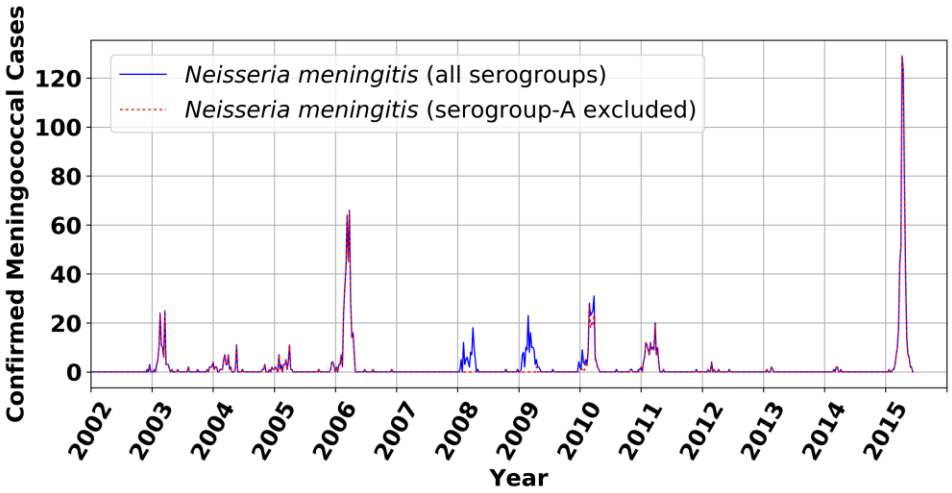

Figure 2: Weekly confirmed meningococcal cases in Niger reported between 2002 to mid-2015, associated to serogroups A, C, W, and X (blue curve), and to serogroups C, W and X (red curve).

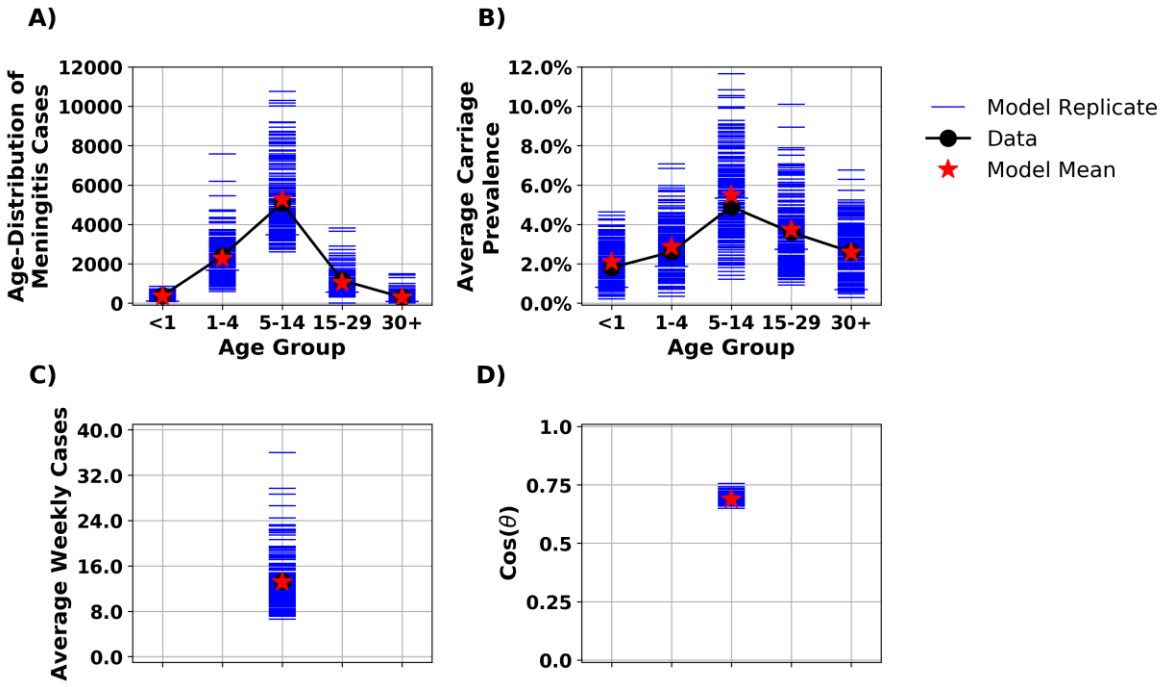

Figure 3: The proposed agent-based model matches the key characteristics of meningococcal epidemics in Niger between 2002 to mid-2015 under the assumption of complete strain replacement. A) Age-distribution of meningococcal meningitis cases in Niger versus the age-distribution of cases generated by the model. B) Estimated meningococcal carriage prevalence in different age groups from carriage survey studies in the African meningitis belt [19] versus the age-specific average carriage prevalence obtained from the model. C) Average of confirmed weekly meningococcal cases observed from 2002 to mid-2015 versus those produced by the model. D) Cosine of the angle ($\boldsymbol{\theta}$) between the vectors of Fourier amplitude for observed and simulated meningitis time-series; cosine of 1 indicates total match in periodicity and cosine of 0 indicates no overlap between the significant periods of two time-series. See Figure S8 in Appendix for the fit of the model under the no strain replacement scenario.

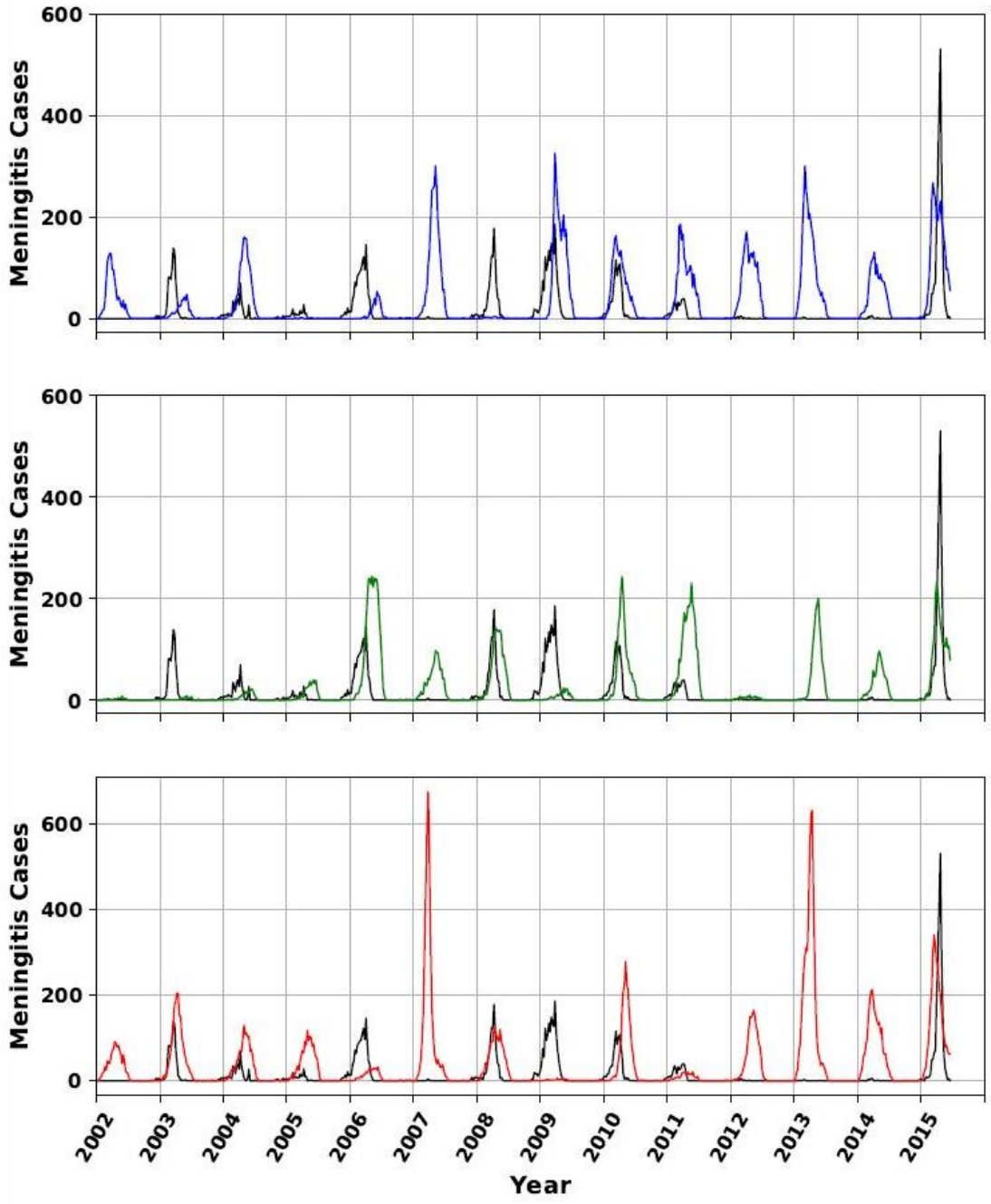

Figure 4: Comparing the time-series of meningococcal cases observed between 2002-2015 in Niger (black curve) with three simulated trajectories produced by the calibrated model (blue, green, and red curves) under "with strain-replacement" scenario. The periodicity at which simulated epidemics are occurring matches the periodicity of observed epidemics. Figure 3, Figure 5 and Figure S9 show that trajectories generated by our model also match other key properties of meningococcal epidemics in Niger (e.g., age-distribution of cases, age-specific carriage prevalence, average weekly meningococcal incidence at national and district level, and number of districts in each year between 2002-2015 where the threshold of 10 meningitis cases per 100,000 population is exceeded).

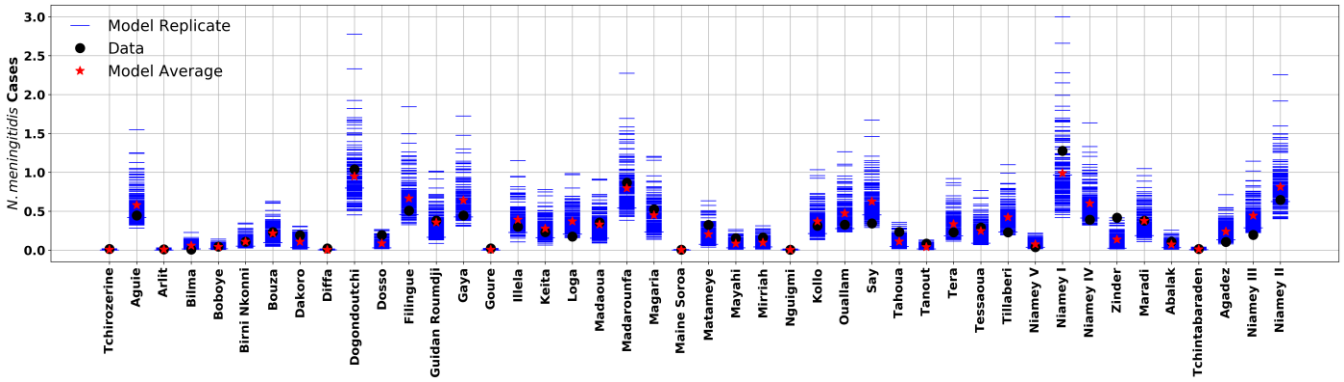

Figure 5: Average weekly *N. meningitidis* cases in Niger's districts produced by our model and observed in the data for the complete strain replacement scenario. See Figure S10 in Appendix for the fit of the model under the scenario of no strain-replacement.

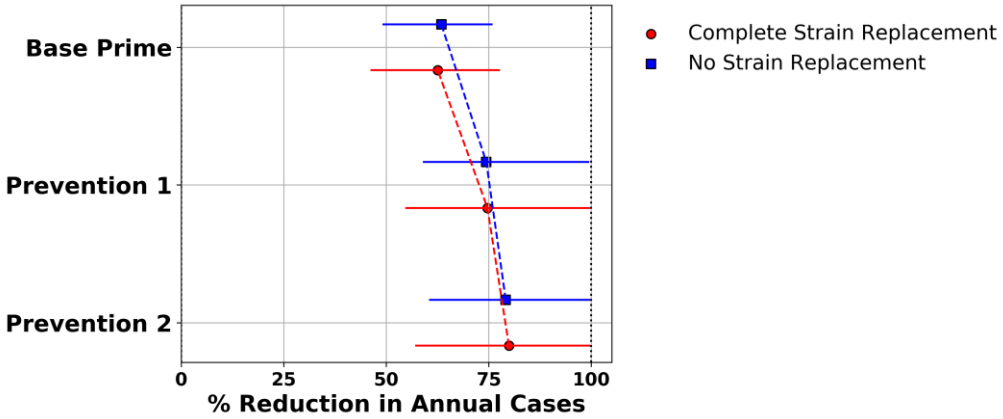

Figure 6: Expected percentage reduction in annual meningococcal cases over a 28-year simulation period for the vaccination strategies described in Table 3 compared to the Base strategy. Bars represent the 95% prediction intervals.

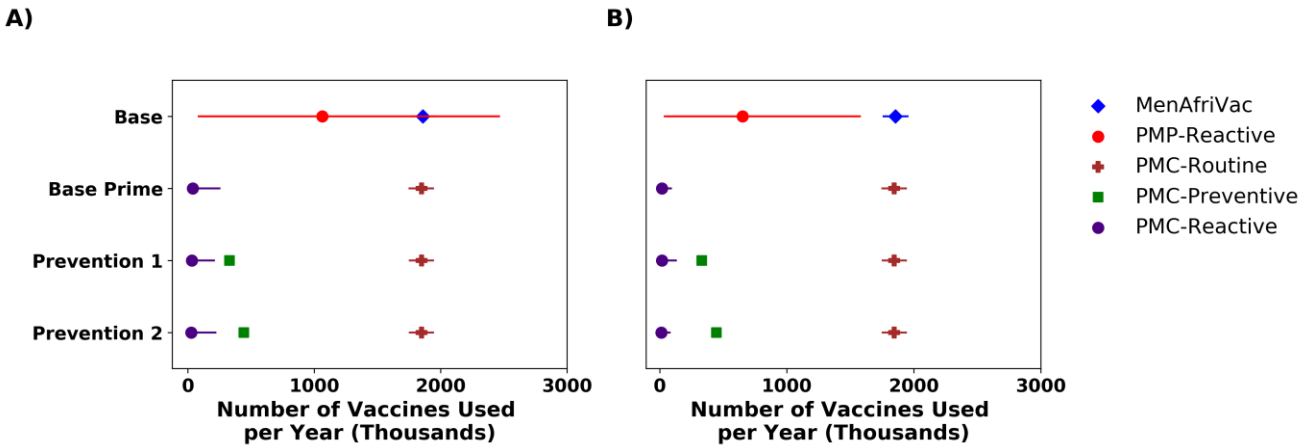

Figure 7: Expected number of vaccines used per year (over a 28-year simulation period). A) Complete strain replacement scenario. B) No strain replacement scenario. We note that preventive campaigns are implemented only once at the beginning of the projection period. Error bars represent 95% projection intervals (error bars that are shorter than the width of symbols are not shown). PMP: polyvalent meningococcal polysaccharide; PMC: polyvalent meningococcal conjugate.

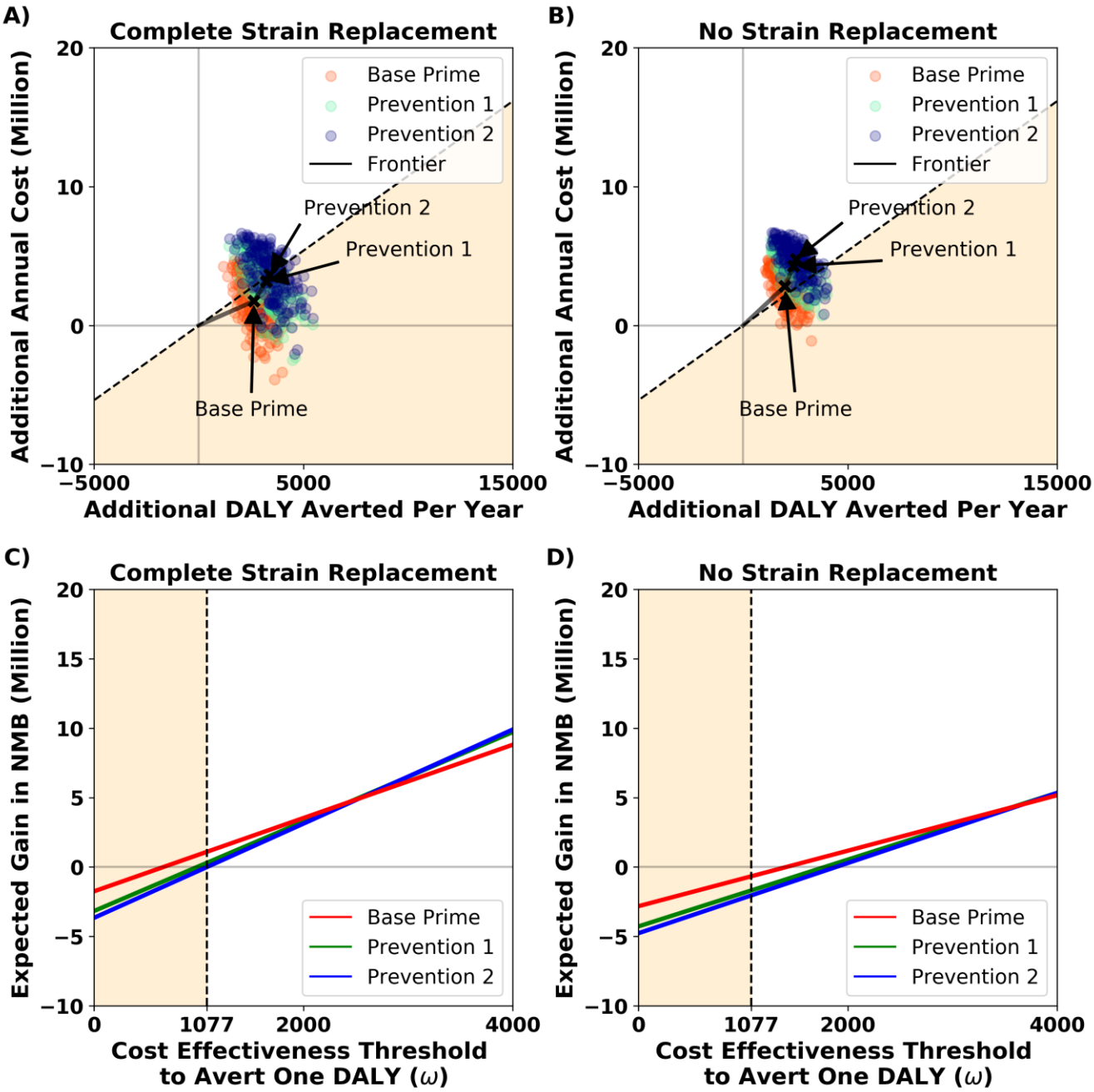

Figure 8: Economic evaluation of vaccination strategies described in Table 3 for the complete strain replacement scenario (A, C) and the no strain replacement scenario (B, D). The price of PMP and PMC vaccines are $4 per dose (see Appendix for sensitivity analysis to the vaccine prices). In figures C and D, the expected gain in net monetary benefit (NMB) of a strategy is calculated with respect to the Base strategy. The dashed line in these figures represents the cost-effectiveness threshold of three per capita gross domestic product of Niger which is estimated to be 1,077 USD in 2015 [45].

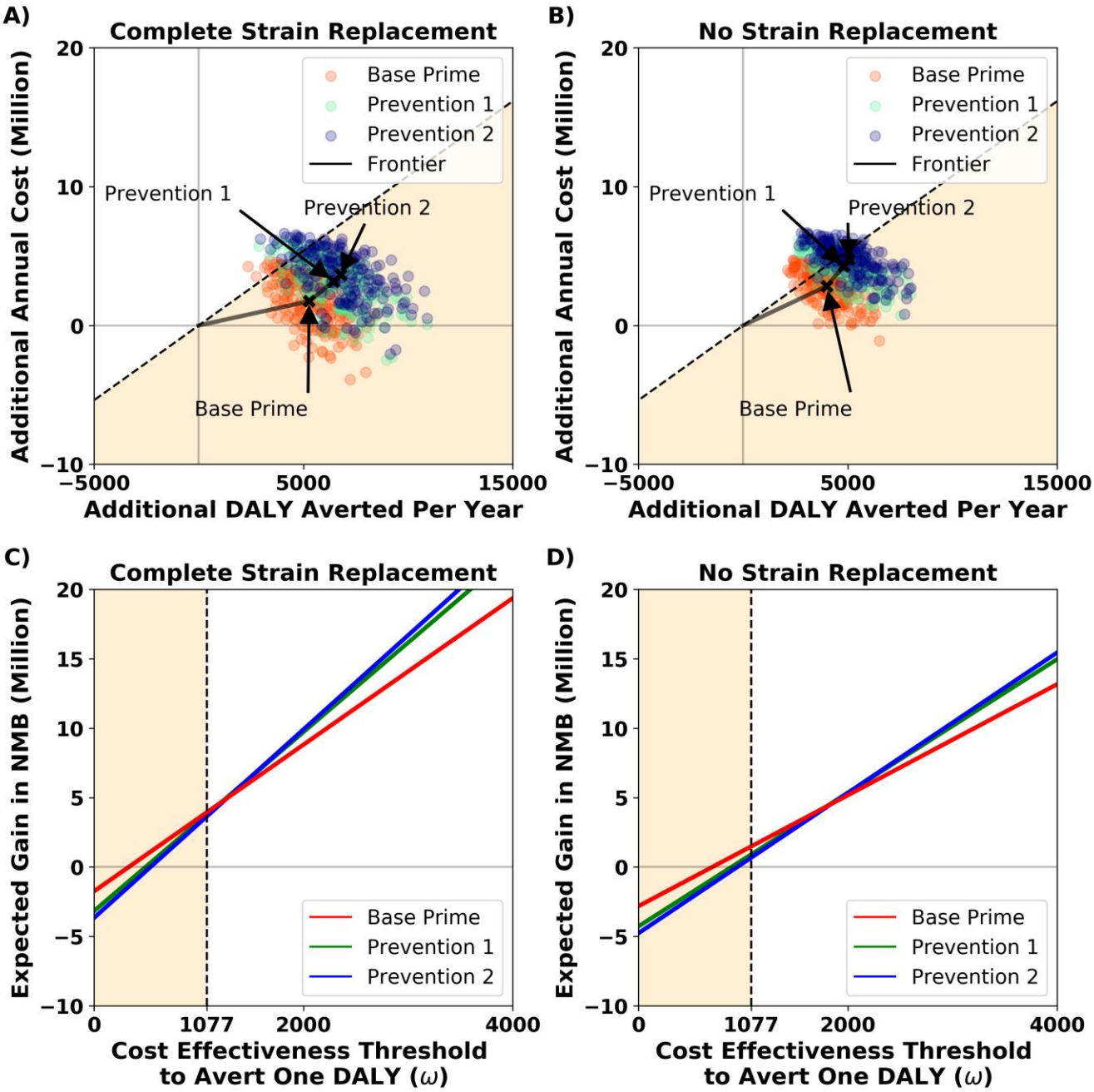

Figure 9: Economic evaluation of vaccination strategies described in Table 3 for the complete strain replacement scenario (A, C) and the no strain replacement scenario (B, D) for the scenario where only 50% of meningococcal cases are reported and correctly categorized. The price of PMP and PMC vaccines are $4 per dose. In figures C and D, the expected gain in net monetary benefit (NMB) of a strategy is calculated with respect to the Base strategy. The dashed line in these figures represents the cost-effectiveness threshold of three per capita gross domestic product of Niger which is estimated to be 1,077 USD in 2015 [45].

Tables

Table 1: Bacteriologic results from spinal fluid (CSF) specimens from cases of suspected meningitis, Niger 2002-2015 [#]

Category	Cases
N. meningitidis	
Group A	3,077
Non-A	2,650
Grouping not done	2,771
Other bacteria[*]	1,777
Positive (but not typed)	5,089
Negative (no conclusive diagnosis)	13,985
Total CSF tested	**29,349**

[#] Data from Centre de Recherche Medicale et Saniteire (CERMES) and the Ministry of Health, Niger.

[*] *S. pneumoniae, H influenzae b, H influenzae nonb, Salmonellae, Micrococcus, S aureus, S epidermidis, Acdnitobacter spp, Bacillus spp*.

Table 2: Vaccination parameters.

Parameter	Vaccine/Vaccination Campaign		Range/Value	Sources
Relative susceptibility to infection compared to unvaccinated*	PMP		[0%-15%]	[29, 51-53]
	PMC		[0%-10%]	[54, 55]
Duration of protection*	PMP	Age [1-4] years	[1-3] years	[53, 56]
		Age 5+ years	[3-5] years	[29, 57]
	PMC		[10-20] years	[39, 55]
Delay between administration of vaccine and the establishment of immunity	PMP or PMC		2 weeks	[58]
Vaccine uptake	Routine[#]		80%-90%	[59]
	Reactive and Preventive (within 10 days)		90%-100%	[60-62]

PMC: Polyvalent meningococcal conjugate; PMP: Polyvalent meningococcal polysaccharide.

* These parameters are sampled for each individual in a simulated trajectory. All other parameters are sampled once per simulated trajectory.

[#] Vaccine uptake for routine vaccination is assumed to be equal to the 9-month measles coverage [59].

Table 3: Alternative vaccination strategies for employing meningococcal vaccines. Adopted from [33].

Strategy	Vaccination Program/Campaign		
	Routine (EPI)	**Reactive**	**Preventive**
Base	*MenAfriVac*™ at 9mo	PMP vaccine for 1-29 yo	-
Base Prime	PMC vaccine at 9mo	PMC vaccine for 1-29 yo	-
Prevention 1[♯]	PMC vaccine at 9mo	-	PMC vaccine for 1-18 yo
Prevention 2[♯]	PMC vaccine at 9mo	-	PMC vaccine for 1-29 yo

EPI: Expanded Program on Immunization; PMC: Polyvalent meningococcal conjugate; PMP: Polyvalent meningococcal polysaccharide.

[♯] If district-level epidemic threshold is exceeded, a reactive campaign using PMC vaccines would be initiated in the district.

Table 4: Cost-effectiveness of alternative vaccination strategies for both strain replacement scenarios.

	Expected Annual Cost (in Million US$)	Expected Annual DALYs	Expected Incremental Annual Cost (in Million US$)	Expected Incremental Annual DALYs Averted	ICER (in US$) per DALY Averted
	Complete Strain Replacement				
Base	**3.64** (0.97, 7.66)	**4,139** (2,240, 6,344)	-	-	-
Base Prime	**5.39** (5.01, 5.84)	**1,499** (536, 2,874)	**1.75** (-1.94, 4.37)	**2,639** (1,642, 3,768)	**662** (-654, 2,473)
Prevention 1	**6.81** (6.47, 7.11)	**917** (11, 2,083)	**1.42** (1.05, 1.76)	**582** (169, 1,428)	**2,437** (696, 6,643)
Prevention 2	**7.3** (6.97, 7.73)	**748** (7, 2,134)	**0.49** (0.18, 0.84)	**169** (-40, 980)	**2,900***
	No Strain Replacement				
Base	**2.5** (0.86, 5.12)	**3097** (1,779, 5,048)	-	-	-
Base Prime	**5.32** (4.99, 5.61)	**1099** (456, 2,189)	**2.82** (0.21, 4.57)	**1,997** (1,200, 3,062)	**1,412** (81, 3,510)
Prevention 1	**6.78** (6.47, 7.05)	**691** (20, 1,573)	**1.46** (1.28, 1.75)	**408** (136, 1,017)	**3,569** (1,343, 11,594)
Prevention 2	**7.27** (6.97, 7.54)	**570** (7, 1,505)	**0.49** (0.21, 0.66)	**121** (-43, 715)	**4,048** (-199,575, 4,732,142)

DALY: disability-adjusted life-year; ICER: incremental cost-effectiveness ratio.
Numbers in parentheses show 95% prediction intervals.
For each vaccination strategy, expected incremental annual cost, DALYs, and ICER are calculated with respect to the left-hand side strategy on the cost-effectiveness frontier shown in Figure 8 (i.e. Base Prime compared to Base; Prevention 1 compared to Base Prime; Prevention 2 compared to Prevention 1).
*95% prediction intervals were unstable because the incremental annual DALYs averted were small for some trajectories.

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